BACKGROUND
- Fragile X syndrome (FXS), a condition driven by a mutation of the FMR1 gene, is the most common single gene cause of autism spectrum disorder (ASD).
- Disruption in the endocannabinoid system as a result of the change in the FMR1 gene, is one of the proposed mechanisms for the symptoms observed in FXS1 and cannabidiol is a non-psychotropic component of this system2.
- ZYN002 (also known as Zigel2) is pharmaceutically produced cannabidiol (not from a plant) that has been uniquely formulated as a gel for transdermal delivery (absorbed through the skin).
- ZYN002 is in clinical development for the treatment of behavioral symptoms associated with FXS, ASD, and 22q11.2 deletion syndrome.
- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities3.
- An FXS-specific version of the ABC-C (ABC-CL-FX), which is more representative of FXS, has been established and has been used to assess changes in behaviors in trials for ZYN002.

RESULTS
BASELINE DEMOGRAPHICS

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Age
- Mean: 9.7 (3-17)

Gender
- Male: 163 (76.3)
- Female: 57 (23.8)

Race
- White: 163 (76.3)
- Asian: 8 (3.3)
- Black or African American: 9 (3.8)
- Native Hawaiian or other Pacific Islander: 1 (0.4)
- Other: 16 (6.7)

Multiple
- 53 (13.4)

Weight
- Median (Min, Max): 35.1 (6-44, 91.8)

Baseline psychotropic medications
- 54%

SAFETY RESULTS
- ZYN002 was safe and well tolerated in the ZYN2-017 trial. Treatment-emergent AEs (TEAEs) were reported by 16% of patients (Table 2). Patients randomized into CONNECT-FX were eligible for entry into ZYN2-017, as those screened for CONNECT-FX but ineligible to continue in the trial.
- Safety data for all enrolled patients with up to 38 months of exposure are reported.
- Safety assessments included adverse events, vital signs (i.e., blood pressure), laboratory tests, electrocardiograms (heart rhythm), and skin assessments at the site of application.
- Skin irritation assessments were scored 0=no redness; 1=minimal redness; 2=moderate redness with sharply defined borders; 3=intense redness with or without swelling; and 4=intense redness with swelling and blistering/broken skin.
- Efficacy data through 15 months for patients with complete (100%) methylation of their FMR1 gene who completed CONNECT-FX are reported.
- The primary efficacy endpoint was change in baseline in the Social Avoidance (SA) subscale of the ABC-C (Table 2).

Figure 1. ZYN2-017 Trial Design and Path of Patient Entry

Figure 2. Sustained Improvement in ABC-C (SA) Subscale in the Full Population, with the Greatest Improvements Seen in Those with Complete Methylation of Their FMR1 Gene

Figure 3. ZYN002-Treated Patients Achieved and Maintained Clinically Meaningful Changes in ABC-C (SA) Social Avoidance in ZYN002 and Placebo Treated Patients Who Switched to Open-Label ZYN002—Patients With Complete Methylation of FMR1

REFERENCES

CONCLUSIONS
- ZYN002 is safe and well tolerated during long term administration.
- ZYN002 led to improvements in ABC-C (SA) Social Avoidance in the full population, with the greatest improvements in patients with complete methylation of their FMR1 gene.
- Patients with complete methylation achieved and maintained clinically meaningful change in Social Avoidance.
- The interim results from this open-label extension trial support the long-term safety and effectiveness of ZYN002 in children and adolescents with Fragile X syndrome, with the greatest improvements seen in those with complete methylation of their FMR1 gene.
- A confirmatory trial, CONNECT-FX, in patients with complete (100%, the primary efficacy population) or partial (<100%) methylation of their FMR1 gene is ongoing (see the poster about CONNECT at this meeting).

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